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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-30 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-30 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948. Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes (see 7. Views).

Applicant is reminded to amend the specification to

16. 35 U.S.C. § 101 reads as follows:
"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

17. Claim 24 is rejected under 35 U.S.C. 101 because the claimed invention is directed toward non-statutory subject matter. Although the preamble of claim 24 is drawn to a computer, it is unclear whether it also recites that this computer is programmed to display a three-dimensional representation of a humanized immunoglobulin on a monitor. If the claim is meant to read on a computer per se (hardware), then it would constitute patentable subject matter. Alternatively, if the claim is meant to read on a mathematical algorithm, a computer program or a physical representation; then this would not be patentable subject matter.

18. Claims 25-30 are rejected under 35 U.S.C. § 101 because the invention as disclosed is inoperative and therefore lacks utility. The specification fails to establish the utility of the claimed humanized 21.6 VLA-4-specific antibody as a pharmaceutical composition for diagnostic and therapeutic methods on human patients.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immune-based drugs can be species- and model-dependent, it is not clear that reliance on the in vitro accurately reflects the relative superiority of the claimed therapeutic strategy.

In addressing antibody-based therapy, Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3)(Tibtech, 1993). Humanized antibodies present serious problems with immunogenicity, since the idiotype of such antibodies will contain unique amino acid sequences. Emery et al. discloses that humanized antibodies are still in the development phase (Exp. Opin. Invest. Drugs, 1994; see entire document). It remains clear that a significant proportion of patients will mount an immune response to the mouse variable region (page 245). Here, the known limitations to clinical efficacy encompassing specificity, binding constants, tissue penetration, clearance rates and the mode of action of the effector are presented (see page 242). Therefore, the art indicates that even humanized antibodies are not necessarily predictable in their efficacy.

In addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, Biotechnology, 1992; see entire document, particularly page 386, column 3, paragraph 4).

It is not clear whether the effectiveness of the claimed humanized VLA-4-specific antibody can be used to detect or treat an ongoing inflammatory response or whether it is effective only in terms of prevention. However, such diseases are diagnosed only after significant tissue damage has occurred. Therefore, it is not clear whether the alleged efficacy of the claimed antibodies could be attributed to the usual scenario of an ongoing disease as well as whether any extrapolation can be made from in vitro or in vivo experimental models.

In addressing therapy for multiple sclerosis, Dijkstra et al. review the limitations of current research and state that no immunosuppressive-based treatments have yet been shown to have a therapeutic index that justifies its widespread administration to MS-patients (1449, #C1; see entire document, including page 128, column 1 paragraph 1).

Applicant has not provided sufficient evidence or nexus a priori that establishes the efficacy of the claimed invention for the disclosed utilities. Therefore, it does not appear that the asserted utility of the claimed compositions and methods for diagnosing or treating humans would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art. See MPEP 608.01 (p).

18. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure and failing to present the best mode contemplated by the applicant for carrying out the invention.

A) Applicant has not disclosed how to use humanized 21-6 antibody as a pharmaceutical composition in diagnostic and therapeutic methods in humans (claims 25-30). The claimed humanized VLA-4-specific antibody is able to bind in vitro. There is insufficient evidence or nexus with respect to the in vivo operability of the claimed humanized antibodies to use applicant's invention for the reasons discussed in detail in the previous rejection made under 35 U.S.C. § 101 (see section 17 above). Therefore, it does not appear that the asserted operability of the claimed methods and compositions would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone.

B) It is apparent that the 21-6 murine antibody and the humanized 21-6 VLA-4-specific antibodies are required to practice the claimed invention as disclosed in the specification and cited in the claims (claims 1-30). Emery et al. states that experience has shown that in addition to the CDRs, amino acids in the framework region also need to be transferred for the process to be successful (see bridging paragraph of pages 245-246). It is noted that no deposit of the appropriate plasmids or the original 21-6 monoclonal antibody (hybridoma) has been made either. As required elements, both the native and humanized 21-6 VLA-4-specific antibodies must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the appropriate hybridoma and clones (e.g. plasmids). See 37 CFR 1.802.

The specification does not provide a repeatable method for obtaining the claimed native and humanized 21-6 VLA-4-specific antibodies and they do not appear to be readily available materials. Deposit of the appropriate hybridoma and clones would satisfy the enablement requirements of 35 U.S.C. 112.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

c) the deposit will be maintained for a term of at least thirty years and at least five years after the most recent request for the furnishing of a sample of the deposited material;

d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 CFR 1.809 (d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements.

20. Claims 1-30 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification (see sections 18-19).

21. Claims 1-30 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-30 are indefinite in that the "group consisting of H27, H28, H29, H30, H44 and H71" should be referred to as the "second" group in claim 1 for proper antecedent basis.

B) Claims 1-30 are indefinite in that line 25 of claim 1 should refer to the "humanized" immunoglobulin rather than the immunoglobulin to distinguish it from the mouse 21-6 immunoglobulin.

C) Claims 1-30 are indefinite in the recitation of "21-6 immunoglobulin" because its characteristics are not known. The use of "21-6 immunoglobulin" as the sole means of identifying the claimed antibody renders the claim indefinite because "21-6" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation to define completely distinct hybridomas and cell lines, for example.

D) Claims 1-30 are indefinite in the recitation of "VLA-4 ligand" because "VLA-4" is the proper specificity. VLA-4 ligand reads on VCAM-1 or fibronectin, while 21-6 binds VLA-4 and not its ligands.

E) Claims 17, 22, 23 and 25-30 are indefinite in the recitation of "binding fragment" because "antigen specific binding fragment" would be more appropriate in defining the metes and bounds of the appropriate fragment.

F) Claim 26 is indefinite in its recitation of the detecting step because it is not clear whether the "target sample" has antecedent basis to both the patient and the tissue sample. Applicant may consider breaking in vitro and in vivo diagnosis into two separate claims for clarity.

The amendments must be supported by the specification so as not to add any new matter.

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

24. Claim 24 is rejected under 35 U.S.C. § 102(b) as being anticipated by a Silicon Graphics IRIS 4D workstation running under the UNIX operating system and using the molecular modelling package QUANTA as acknowledged in the specification (page 31, paragraph 1) and Kettleborough et al. (Protein Engineering, 1991, page 774, column 2, paragraph 1). The specification also acknowledges that computer hardware and software for producing three-dimensional images of immunoglobulin molecules are widely available (page 14, lines 19-20).

As recited, the computer is a product irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

25. Claims 1-27 and 29 are rejected under 35 U.S.C. § 103 as being unpatentable over Monshizadegan et al. (Agents Actions, 1993) and Wayner (WO 91/03252) in view of Queen et al. (1449, #B3; PCT 90/07861) and Kettleborough et al. (1449, #C3; Protein Engineering, 1991). Claims 1-27 are drawn to humanized 21-6 VLA-4-specific antibodies, nucleic acids that encode these proteins as well as their use in diagnostic and therapeutic methods. Claim 24 is drawn to a computer that displays such humanized antibodies.

Monshizadegan et al. teach the 21-6 VLA-4-specific antibody and its ability to inhibit α4 integrin function of the instant invention (see entire document). It is noted that this was presented at the Sixth International Conference of The Inflammation Research Association. This reference differs from the instant claims by not teaching the humanization of the 21-6 monoclonal antibody.

Wayner et al. teach deriving α4β1-specific antibodies for various in vitro and in vivo diagnostic and therapeutic utilities, which are encompassed by the claims (see entire document). Since the α4β1-specificity is the same as VLA-4, it is not clear what critical differences exist between the claimed and referenced antibodies. Wayner et al. differs from the instant claims by not teaching the humanization of antibodies per se.

Both Queen et al. and Kettleborough et al. teach the art-known and claimed procedures to humanize a monoclonal antibody, including the appropriate vectors, nucleic acids, modelling procedures and computers that achieve appropriate specificity and affinity for diagnostic and therapeutic uses (see entire documents). Here, the art-known advantage of humanizing antibodies for reducing immunogenicity of murine antibodies and providing human immunoglobulin effector function was stated.

One of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of humanizing VLA-4-specific antibodies including the 21-6 monoclonal antibody as a diagnostic and therapeutic tool in treating human disease. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

26. Claims 28 and 30 are rejected under 35 U.S.C. § 103 as being unpatentable over Monshizadegan et al. (Agents Actions, 1993), Wayner (WO 91/03252), Queen et al. (1449, #B3; PCT 90/07861) and Kettleborough et al. (1449, #C3; Protein Engineering, 1991) as applied to claims 1-27 and 29 above and in further view of Yednock et al. (1449, #C4; Nature, 1992). Claims 28 and 30 are drawn to the use of humanized 21-6 VLA-4-specific antibodies for treating multiple sclerosis and inflammation in brain tissue.

Monshizadegan et al., Wayner, Queen et al. and Kettleborough et al. have been discussed supra in section 25. These references differ from the claimed invention by not teaching treating

inflammation in nervous tissue per se.

Yednock et al. teach the application of VLA-4-specific antibodies in the treatment of experimental encephalomyelitis as a model of multiple sclerosis (see entire document).

One of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of humanized VLA-4-specific antibodies including the 21-6 monoclonal antibody in the treatment of inflammatory nervous tissue. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

29. No claim is allowed.

30. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. David Lacey can be reached on (703) 308-3535. The fax phone number for Group 180 is (703) 305-3014 or (703) 308-4227. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
September 21, 1994

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
9/22/94